REMARKS

Claims 30, 31, 39, 41, 52, and 55 have been amended. Claims 38, 50, 51, 53, and 54 have been canceled. Claims 30-37, 39-45, 52, and 55 are pending in the present application.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments and the following remarks is requested.

I. The Rejection of Claims 30, 31, 36, 38, 40, and 42-45 under 35 U.S.C. § 112, First Paragraph

Claims 30, 31, 36, 38, 40, and 42-45 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Office Action states:

> It is acknowledged that the art teaches how to make variant polynucleotides and how to test a polypeptide for carboxypeptidase activity. It is also acknowledged that robotics enhance the speed at which enzymes can be produced and assayed for activity. However, the vast majority of the polypeptides encompassed by the scope of the current claims will not have carboxypeptidase activity. The specification fails to provide any guidance for the selection of which of the infinite number of variants have the claimed activity. Without such guidance, one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute **undue** experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification. Therefore, rejection is maintained.

This rejection is respectfully traversed for reasons of record and additional reasons set forth below.

The present invention is directed to isolated nucleic acid sequences encoding a polypeptide having carboxypeptidase activity, selected from the group consisting of:

(a) a nucleic acid sequence encoding a polypeptide having an amino acid sequence which has at least 95% identity with amino acids 19 to 555 of SEQ ID NO. 2;

(b) a nucleic acid sequence having at least 95% homology with nucleotides 55 to 1662 of SEQ ID NO. 1; and

(c) a nucleic acid sequence which hybridizes under high stringency conditions with nucleotides 55 to 1662 of SEQ ID NO. 1, or its complementary strand, wherein high stringency conditions are defined as prehybridization and hybridization a 42°C in 5X SSPE, 0.3% SDS, 200 mg/ml sheared and denatured salmon sperm DNA, and 50% formamide.

Applicants disagree with the Office's following statement: "The specification fails to provide any guidance for the selection of which of the infinite number of variants have the claimed activity. ... This would clearly constitute **undue** experimentation."

The Office Action states: "It is acknowledged that the art teaches how to make variant polynucleotides and how to test a polypeptide for carboxypeptidase activity. It is also acknowledged that robotics enhance the speed at which enzymes can be produced and assayed for activity. However, the vast majority of the polypeptides encompassed by the scope of the current claims will not have carboxypeptidase activity. The specification fails to provide any guidance for the selection of which of the infinite number of variants have the claimed activity."

Applicants respectfully disagree with the conclusion that the specification "fails to provide any guidance for the selection of which of the infinite number of variants have the claimed activity." Applicants describe in the instant specification methods for producing the carboxypeptidases (page 26, line 26, to page 27, line 24); and for purifying the carboxypeptidases and characterizing the properties of the encoded carboxypeptidases (Examples 1-3). Applicants also describe methods for preparing and probing DNA libraries (Example 4-7); for isolating nucleic acids encoding the carboxypeptidases (Example 7); for determining cross-hybridization of the nucleic acids encoding carboxypeptidases using nucleotides 55 to 1662 of SEQ ID NO: 1, or their complementary nucleotides (Example 9); for comparing the percent identity of the deduced amino acid sequences of the carboxypeptidases to amino acids 19 to 555 of SEQ ID NO: 2 using the Clustal method according to Higgins, 1989, *CABIOS* 5: 151-153 (Example 8); and for determining the degree of homology between two nucleic acid sequences using the Clustal method according to Higgins, 1989, *supra* (page 12, lines 14-20).

Based on Applicants' specification, it is well within the art to select which of the variants, which have at least 95% identity with amino acids 19 to 555 of SEQ ID NO. 2, or which are encoded by a nucleic acid sequence having at least 95% homology with nucleotides 55 to 1662 of SEQ ID NO. 1 or which hybridize under high stringency conditions with nucleotides 55 to 1662 of SEQ ID NO. 1, or its complementary strand, and have the claimed carboxypeptidase activity.

To further prosecution, Applicants have amended claim 30 in part to recite "95% identity with amino acids 19 to 555 of SEQ ID NO. 2", "a nucleic acid sequence having at least 95% homology with nucleotides 55 to 1662 of SEQ ID NO. 1", and "a nucleic acid sequence which

hybridizes under high stringency conditions with nucleotides 55 to 1662 of SEQ ID NO. 1, or its complementary strand".

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

II. The Rejection of Claims 30, 31, 36, 38, 40, and 42-49 under 35 U.S.C. § 112, First Paragraph

Claims 30, 31, 36, 38, 40, and 42-49 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Office Action stated:

> The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification fails to disclose polynucleotides (i) encoding residues 19-555 of SEQ ID NO: 2 (ii) encoding a polypeptide having 80%, 85%, 90% or 95% identity with residues 19-555 of SEQ ID NO: 2, (iii) that hybridize with residues 55-1662 of SEQ ID NO: 1, or (iv) encoding a polypeptide having 85% identity with SEQ ID NO: 2. As such, 30, 31, 35, 38, 39, 40, and 50-53 introduce New Matter and are, thus, rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the Written Description requirement..

This rejection is respectfully traversed for reasons of record and additional reasons set forth below.

The Office alleges that the specification fails to disclose polynucleotides encoding residues 19-555 of SEQ ID NO: 2. Applicants disagree. SEQ ID NO: 1 encodes amino acid residues 19-555 of SEQ ID NO: 2.

The Office alleges that the specification fails to disclose polynucleotides encoding a polypeptide having 80%, 85%, 90% or 95% identity with residues 19-555 of SEQ ID NO: 2. Applicants disagree. As stated in the Amendment of May 14, 2004, Federal Circuit decisions provide that a specification complies with the written description requirement if it provides "a precise definition, such as by structure, formula, chemical name, or physical properties of the claimed subject matter sufficient to distinguish it from other materials." See, e.g., *University of California v. Eli Lilly and Co.*, 43 U.S.P.Q.2d 1398, 1404 (Fed. Cir. 1997); *Enzo Biochem v. Gen-Probe Inc.*, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002). In fact, "[a] description of a genus of cDNAs may be achieved by means of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Eli Lilly and Co.*, 43 U.S.P.Q.2d at 1569.

It is well established in the art that the definition of a genus of genes encoding polypeptides

having an enzyme activity of interest is accomplished by using structural features that show the relatedness of the genes and their encoded products. For decades the scientific community has employed three structural features to define the relatedness of genes and their products. The three structural features are (1) percent identity of the amino acid sequences encoded by the genes, (2) percent homology of the nucleic acid sequences of the genes, and (3) nucleic acid hybridizations under defined stringent conditions to identify complementary strands of genes encoding the same or similar enzyme or protein function. These structural features have been used to predict the function of polypeptides encoded by novel genes, and to place them in an existing genus.

Limiting the literal scope of protection of such a new genus or family to the nucleic acid sequence of SEQ ID NO: 1 or the amino acid sequence of SEQ ID NO: 2 provides little incentive to an Applicant to seek patent protection because biological diversity dictates that there will be natural variation in the sequences of other homologous genes existing in nature that are structurally- and functionally-related. Biological diversity in a given gene sequence can easily be found. As genes that fulfill a similar function in different species have evolved from a common ancestor, natural variation in the nucleic acid sequence will rapidly evolve following this speciation. Sequence variation within a single species is also common. Alternatively, the skilled artisan could easily circumvent the literal scope of protection by preparing a variant containing an insertion or deletion of one or more amino acid residues and/or the substitution of one or more amino acid residues by different amino acid residues.

In the claims at issue, Applicants provide a recitation of three structural features common to the claimed genus: (1) a nucleic acid sequence encoding a polypeptide having an amino acid sequence which has at least 95% identity with amino acids 19 to 555 of SEQ ID NO: 2; (2) a nucleic acid sequence having at least 95% homology with nucleotides 55 to 1662 of SEQ ID NO: 1; and (3) a nucleic acid sequence which hybridizes under high stringency conditions with nucleotides 55 to 1662 of SEQ ID NO: 1 its complementary strand

The structural features are described on page 4, line 21, to page 8, line 2, and page 12, lines 14-20, of the specification. As mentioned above, the three structural features of percent identity at the deduced amino acid sequence level, percent homology at the DNA level, and the ability of the claimed nucleic acid sequence to hybridize under specific stringency conditions have been used for decades by persons of ordinary skill in the art to determine the relatedness of proteins and their genes with respect to structure and function to ascertain whether they belong to the same genus or family. The scientific literature abounds with disclosures of these three structural features to describe the relatedness of proteins and their genes as well as to

distinguish a protein and its gene from other proteins and their genes. Moreover, annotated databases of families of structurally-related proteins with a specific biological activity have been constructed based on these structural features. For example, the CAZy database describes the families of structurally-related catalytic and carbohydrate-binding modules (or functional domains) of enzymes that degrade, modify, or create glycosidic bonds. See www.afmb.cnrs-mrs.fr/CAZY/.

It is well established in the art that there is a definitive relationship between protein function and % identity or homology at either the nucleotide or amino acid level. Percent identity is highly predictive of protein function and without this tool it would be impossible to make meaningful annotations of genomes in sequencing projects. Proteins that share 90% amino acid identity are known to possess the same catalytic/biochemical function which has formed the basis for genome annotation and comparative genomics. In fact, 90% identity is an extremely conservative criterion for judging functional similarity. A long history of structure-function studies has demonstrated that single domain proteins that share substantial similarity (and >30% identity) over their entire length (>80 residues) without introduction of numerous gaps are almost certainly homologous (derive from a common evolutionary ancestor) and share the same three-dimensional structure. At the 95% level of amino acid identity, orthologous enzymes in related species are virtually guaranteed to share the same catalytic function and substrate specificity. Likewise, genes that share 95% homology encode proteins with the same catalytic/biochemical function. A simple search of any public database using the criteria above for a reference protein of interest will prove that there is a definitive relationship between protein function and % identity or homology at either the nucleotide or amino acid level.

In fact, the PTO has determined that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... *i.e.,* complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure,* or some combination of such characteristics." Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, 66 Fed.Reg. 1099, 1106 (Jan. 5, 2001).

In the claims at issue, each of the claimed structural features (percent identity, percent homology, and hybridization) specifies a family of structurally- and functionally-related enzymes having carboxpeptidase activity. Since the claimed structural features provide a correlation between function and structure, the written description requirement is satisfied.

The Office alleges that the specification fails to disclose polynucleotides that hybridize with residues 55-1662 of SEQ ID NO: 1. Applicants disagree. Example 9 of the specification discloses polynucleotides that hybridize with residues 55-1662 of SEQ ID NO: 1 as shown in Table 2.

As stated in Section I, to further prosecution, Applicants have amended claim 30 in part to recite "95% identity with amino acids 19 to 555 of SEQ ID NO. 2", "a nucleic acid sequence having at least 95% homology with nucleotides 55 to 1662 of SEQ ID NO. 1", and "a nucleic acid sequence which hybridizes under high stringency conditions with nucleotides 55 to 1662 of SEQ ID NO. 1, or its complementary strand".

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

III. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

Date: October 21, 2004

Robert L. Starnes, Ph.D.
Reg. No. 41,324
Novozymes Biotech, Inc.
1445 Drew Avenue
Davis, CA 95616-4880
(530) 757-4715